REMARKS

This case contains claims 1-5 with the entry of this Amendment. Claim 1 has been amended for improved clarity. Claims 4 and 5 have been added to better claim the subject matter that Applicant regards as the claimed invention. Support is found in the Specification, on page 4, lines 3-8, and page 5, lines 1-4, respectively. Therefore, none of the amendments made herein constitutes the addition of new matter.

Rejection under 35 U.S.C. §112:

Claims 1-3 are rejected under 35 U.S.C. §112, first paragraph, on the grounds that the Specification, while being enabled for a method for preparing a factor VIII molecule having modified glycosylation wherein a specific mutation in the A2 domain of a factor VIII protein is made specifically by replacing leucine 486 of SEQ ID NO:2 with asparagine, allegedly does not reasonably provide enablement for a method for preparing a factor VIII protein having modified glycosylation comprising making a mutation anywhere in the protein sequence, or anywhere in the A2 or C2 domains to insert a glycosylation site. It is further alleged that undue experimentation would be required to practice the claimed method to successfully produce a functional factor VIII protein having the structural limitations of the claims in the present case. Applicant respectfully traverses this rejection.

The claimed invention is a method for preparing a factor VIII having modified glycosylation. Amended claim 1 specifically defines that the modified factor VIII prepared according to the claimed method be biologically active, less immunogenic and antigenic than the unmodified factor VIII when administered in vivo. This invention was based on the inventor's discovery that the inhibitory antibodies to factor VIII present in certain hemophiliac patients bind to either the A2 or C2 domains and disrupt specific functions associated with these domains. In order to reduce the antigenicity and immunogenicity of factor VIII, the inventor applied the knowledge obtained from the HIV studies; when the immune system of the HIV-infected subject akes antibodies to the glycosylated epitope on the exterior of HIV, the virus escapes the immune surveillance of the host by mutating the glycosylation sites. Based on this information, the inventor developed the claimed method of preparing a low immunogenic and low antigenic factor VIII by introducing a mutation for the consensus amino acid sequence for N-linked glycosylation.

Applicant points out that the Specification provides specific examples of the modified factor

VIII having the introduced consensus site (N-X-S/T) for N-glycosylation; leucine (L) at the amino acid residue 486 in the A2 domain was replaced with asparagine (N) and glutamine (Q) at the amino acid residue 2189 in the C2 domain with asparagine (N). Factor VIII with L486N modification was shown to be biologically active as stated in the Specification on page 4, lines 29-30. The biological activity of a mutated factor VIII can easily be measured in an in vitro assay as is well known in the art. To practice the claimed invention, a person of ordinary skill in the art selects a desired segment of factor VIII, introduces a mutation to create the consensus site of N-X-S/T, expresses such a mutated factor VIII, and tests for its biological activity as well as the reduced immunogenicity and antigenicity. Experimental protocols necessary for practicing the claimed invention are readily available in the art. The relative skill of those in the art is high. The number of experimentation may be high but the experimentation necessary to make the modified factor VIII of this application is routine not undue.

The Office Action states that Aly et al. indicate that the introduction of glycosylation sites at certain positions of the factor VIII molecule inactivate the protein but do not propose how the glycosylation affected the procoagulant activity. It is further alleged that due to the complexity of factor VIII structure, undue experimentation is necessary for a skilled artisan to determine what amino acid positions in the factor VIII sequence could be modified to insert a glycosylation site that would result in an active factor VIII protein.

Applicant submits that the above allegation is not justified in the present case for the following reasons.

As discussed above, the object of the claimed invention is to provide a modified factor VIII that is biologically active but shows reduced immunogenicity and antigenicity when administered to the patients deficient in factor VIII. When the present application was filed, it was known that the inhibitory antibodies present in certain hemophiliac patients reacted with the epitopes in the A2 and C2 domains of factor VIII. The inventor of the present application thus combined this information with the finding that the glycosylation status changes the antigenicity and/or immunogenicity of certain viral surface proteins. As pointed out by the Examiner, the level of skill in the relevant art is high. The biology of factor VIII was well established at the time when this application was filed and numerous assays to measure the biological activity of factor VIII were readily available in the art.

In summary, Applicant submits that a person of ordinary skill in the art can make the claimed

modified factor VIII that is biologically active, less immunogenic and antigenic than the unmodified factor VIII, based on the teachings provided in the Specification, combined with the knowledge available in the art. Based on the foregoing, withdrawal of the rejection under 35 U.S.C. 112, first paragraph, is respectfully requested.

In conclusion

Based on the foregoing amendments and arguments, this case is considered to be in condition for allowance and passage to issuance is respectfully requested.

If there are any outstanding issues related to patentability, the courtesy of a telephone interview is requested, and the Examiner is invited to call to arrange a mutually convenient time.

This amendment is accompanied by a Petition for Extension of Time (one month) and a check in the amount of $110.00 as required under 37 C.F.R. 1.17(a)(3) for a large entity. If the amount submitted is incorrect, however, please charge any deficiency or credit any overpayment to Deposit Account No. 07-1969.

Respectfully submitted,

Heeja Yoo-Warren
Reg. No. 45,495

GREENLEE, WINNER AND SULLIVAN, P.C.
5370 Manhattan Circle, Suite 201
Boulder, CO 80303
Telephone: (303) 499-8080
Facsimile: (303) 499-8089
E-mail: winner@greenwin.com

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1. (Once amended) A method for preparing a biologically active factor VIII having modified glycosylation comprising the steps of

mutating a desired segment of factor VIII DNA to encode –N-X-S/T, where N is asparagines, X is any amino acid and S/T is serine or threonine, thereby providing mutated factor VIII DNA encoding a post-translational glycosylation site at the desired locus of factor VIII protein, and

expressing the mutated DNA in a host cell capable of post-translational glycosylation, whereby biologically active factor VIII having modified